REMARKS

Enclosed is the Information Disclosure Statement listing the publication reference cited in the previously filed amendment.

Claim Rejections under 35 USC §112

Claims 1-20 have been rejected under 35 USC 112, first paragraph.

The action states that no literal or figurative support could be found for the statement "longer than 7 days at levels 20% higher than the nucleic acid sequence present in a circular or supercoiled nucleic acid" and that the statement therefore constitutes new matter. That this limitation was specifically contemplated is provided in the specification on page 15 lines 14-16. In example 5, expression of the transgene at day 7 in animals transfected with the linear expression vector is 13 times (1300%) that of expression of the same transgene in animals transfected with the circular expression vector. At days 28 and 62, expression in animals transfected with the linear expression vector is, respectively, 137 and 385 times that of expression of the transgene in animals transfected with the circular expression vector. All of these values represent increases in expression of greater than 20% when the expression cassette is delivered as a linear vector. Therefore, it is the applicants' opinion that "expression of the transgene from the linear nucleic acid expression vector persists for at least 7 days at levels higher than would be produced from the same transgene present in a circular or supercoiled nucleic acid" is fully supported by the specification.

The action also states that the specification fails to provide any guidance on any particular elements comprised by the nucleic acid sequences being delivered that would result in expression for an extended period of time. Applicants respectfully disagree. Applicants show in example 5 on pages 22-23, that delivery of a circular plasmid DNA vector to a mouse results in transient expression of an encoded transgene. In contrast, digestion of the plasmid vector (example 2 on pages 21-22) and delivery of the expression cassette as a linear DNA vector results in much greater transgene expression levels at days 7, 28 and 62, i.e. "for an extended period of time". Since both the plasmid (circular) and linear DNA vectors contain identical transgene expression cassettes, one can conclude that the linear vector provides for longer term expression of transgenes *in vivo*. Applicants specify a non-viral linear DNA vector in the amended claims, which is supported on page 8 line 14 and page 19 lines 6-19 of the specification.

In a subsequent publication, data from Chen et al. 2001 (IDS reference) confirmed these results using other promoters and transgenes (see page 404, second column, under Results subheading). Specifically, Chen et al. showed increased long term expression with linear DNA vectors containing a Rous sarcoma virus long terminal repeat promoter and an ApoE enhancer / hepatic control region / α1-antitrypsin promoter. They observed long term expression with the human α1-antitrypsin and human factor IX transgenes, respectively.

Applicants have shown that delivery of an expression cassette on a linear DNA vector provides longer term expression of a transgene in a mammal. Subsequent literature in refereed scientific journals supports this claim.

The action states, on page 7, that the claim is indefinite because it would be necessary to provide a relative comparison to know if one were infringing the claim. Applicants have amended the claim to obviate the rejection. Support for "long term *in vivo* expression" and "expression of the transgene persists for an extended period of time" can be found in the specification on page 8 lines 13-14, page 15 lines 14-16, page 19 line 6-23, example 5 on pages 22-23 and in the abstract.

Claim rejections under 35 USC §102

Claims 1-4, 7, 18 and 19 have been rejected under 35 USC 102 (b) as being anticipated by Wolff et al. 1990. Applicants have amended claims 1 and 18 to cite delivery of a non-viral linear DNA vector. Wolff teaches a method for delivery of RNA to a cell. Wolff et al. do not teach long-term expression or delivery of a non-viral linear DNA vector. Delivery of RNA, which is inherently less stable the DNA, and expression within several hours does not constitute long term expression as taught in the specification. The action states that because the RNA delivered by Wolff et al. has different sequences at the 5′ and 3′ ends, it would be considered to have chimeric ends. Applicants respectfully disagree. Claim 8 specifically cites the chimeric ends are "derived from Tn5 transposase recognition elements." Any two different sequences does not meet the limitation of "derived from Tn5 transposase recognition elements."

The action states on page 11 that a single stranded RNA molecule could be considered to be blunt ended and sticky ended. Applicants respectfully disagree. The terms "blunt ended" and

"sticky ended" are recognized terms in the art that specifically refer to double stranded nucleic acids. Either the double stranded nucleic acid terminates in a base pair (blunt ended) or the double stranded nucleic acid terminates with one strand having unpaired nucleotides (sticky ended).

The action states on page 11 and on page 16 that Wolff et al. and Budker et al. teach the limitation of delivering a linear DNA expression vector because they describe the use of restriction enzyme digestion in generating vectors. Applicants respectfully disagree. Neither Wolff et al. nor Budker et al. deliver the restriction enzyme digested nucleic acid fragments directly into cells as linear DNA vectors. Both Wolff et al. and Budker et al. first clone the linear DNA products into plasmids. The resultant plasmids are circular DNA molecules. Wolff et al., Budker et al. and Sambrook et al. describe the use of restriction fragments and PCR generated DNA fragments in molecular applications such as molecular cloning as the examiner states. However, the use of DNA fragments in the process of molecular cloning and plasmid generation is not equal to teaching the delivery of these fragments to cells to obtain long term transgene expression.

Claims 1, 2, 5, 7-13, 18 and 19 have been rejected under 35 USC 102 (b) as being anticipated by Goryshin et al 2000. Goryshin et al. teach delivery of a transposition complex (DNA + transposase) to bacteria and yeast. Goryshin et al. observed no expression when the DNA vector was delivered in the absence of the transposase (page 98, Table 1; page 99, second full paragraph). Therefore, Goryshin et al. taught that delivery of a linear DNA vector to a cell in the absence of transposase fails to result in expression of a transgene in bacteria and yeast. Also, Goryshin et al. did not teach delivery of a non-viral linear DNA vector to a cell in a mammal.

The action states on page 11 that Goryshin teaches that the transposon sequences used are mosaic, indicating they are not the same. Applicants point out that the term mosaic, as used by Goryshin, indicates that the sequences are an art recognized Tn5 transposase binding element made by modification of three bases of the wild type outside element, and not that the sequences are different.

Claims 1, 2, 5, 7-13, 18 and 19 have been rejected under 35 USC 102 (b) as being anticipated by Tucker et al. 1992. Similarly to Goryshin, Tucker et al. teach a method for delivering a

transgene to a bacterial cell. Tucker et al. also teach that the DNA vector must encode a transposase. It is the applicants' opinion that Tucker et al. do not teach delivery of a non-viral linear DNA vector to a cell in a mammal or delivery of a DNA vector that does not encode a transposase. Claims 1 and 17 of Tucker et al. cite delivery of a plasmid to a bacterial cell. By definition, a plasmid is a circular DNA molecule. Therefore, Tucker et al. do not teach a linear DNA vector. Claim 16 of Tucker requires conjugation by another bacterial cell to deliver the genes to a bacterial cell. The teaching of Tucker is thus limited to delivery of nucleic acid to bacterial cells, which is vastly different than delivery to mammalian cells *in vivo*.

The action states on pages 12 and 15 that Tucker et al. teach in column 6 lines 19-25 that the vector is "preferably a linear polypeptide." Applicants believe that the Examiner is referring to Reznikoff et al. (6,159,736, issued 2000). Reznikoff et al. teaches a method for making insertional mutations. Reznikoff does not teach delivery of a linear DNA vector to a cell in a mammal in order to obtain long term expression of a transgene.

Claims 1, 16, 17 and 18 have been rejected under 35 USC 102 (b) as being anticipated by Rolland et al. 2003. Rolland et al. teach a method of formulating nucleic acid for delivery *in vivo*. More specifically, Rolland et al. state, "...it would be desirable to formulate nucleic acids with compounds which would retard the rate at which nucleic acids diffuse or are carried away from a site at which cellular uptake of the nucleic acid is desired." (column 1 lines 49-52). Rolland et al. also state, "This invention features compositions and methods for enhancing the administration to and uptake of nucleic acids by an organism." (column 1 lines 60-21). It is the Applicants' opinion that because Rolland et al. teach a method of formulating nucleic acid, they supply a list of all known forms of nucleic acids which can be formulated according to their invention. However, Rolland et al. provide no teaching or motivation for choosing one form of nucleic acid vs. another form of nucleic acid to achieve long term expression in a mammal. In fact, Rolland et al. teach away from delivering linear DNA to cells in mammals in order to achieve expression of the transgene in the mammal (see page 15 lines 23-25). It is noted that the references cited by Rolland et al. investigated short term expression rather than long term expression.

The action states on pages 13 and 15 that it is known in the art that cDNA and RNA are linear nucleic acid molecules. Applicants respectfully disagree. The term cDNA is used in the art to

indicate the type of nucleic acid sequence and not the topological structure of the nucleic acid. Complementary DNA (cDNA) gets it name from the fact that it represents sequence that is complementary to a mature messenger RNA sequence transcribed from a gene and does not contain the intron sequences present in a genomic copy of a gene. cDNA may be present as a linear nucleic acid molecule or is my be cloned into a plasmid and thus be present in a circular nucleic acid molecule. Likewise, the term RNA does not require that the nucleic acid molecule be linear. While messenger RNA (mRNA) is linear, some RNA viruses contain a circular RNA genome.

Claim rejections under 35 USC §103

Claims 1, 7, 14, 15, 18 and 19 have been rejected under 35 USC 103(a) as being unpatentable over Rolland et al. in view of Budker et al. 1998. Cliams 1, 6, 18 and 20 have been rejected under 35 USC 103(a) as being unpatentable over Tucker et al. in view of Sambrook et al. 1989). Applicants believe the amended claims are not obvious in light of Rolland and Tucker for the reasons stated above in response to the claim rejections under 35 USC §102.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that amended claims 1 and 18 and dependent claims 2-17 and 19-20 should be allowable.

Respectfully submitted,

Mark K. Johnson Reg. No. 35,909
Mirus
505 South Rosa Road
Madison, WI 53719
608-238-4400

I hereby certify that this correspondence is being sent by facsimile transmission at 703-308-4242 to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450 on this date: Dec. 22, 2003.

Kirk Ekena